AMENDMENTS TO THE SPECIFICATION

Please amend paragraph [0105] of the published application as follows:

- - The molecule having the antigen-binding portion of an antibody according to the present invention can be used in a method for blocking the ligand-dependent activation and/or ligand independent (constitutive) activation of FGFR3. Preferred embodiments of such antibodies/molecules, obtained from an antibody library designated as HUCAL~~HuCAL~~® (Human Combinatorial Antibody Library) clone, is presented in Table 1A with the unique V_H-CDR3 and V_L-CDR3 sequences given. - -

Please amend paragraph [0131] of the published application as follows:

- - In addition to sequencing of the clones, a series of biochemical assays were performed to determine affinity and specificity of the molecules to the respective receptors. Table 1C lists the affinity of the respective molecules to FGFR3 and FGFR1 as measured by BIACORE~~BIAcore~~®-and/or FACS. In a binding assay to FGFR3-expressing cells, the IC_{50} of the molecules was calculated (Example 6). Domain specificity was determined as described in Example 8. The ligand-independent inhibition of FGFR3 (neutralizing activity) was determined as described in Example 10. Finally, the molecules were synthesized in a number of different formats including Fab, miniantibody (Fab-dHLX), IgG1, IgG4, IgG3 and as single chain Fv (scFv). - -

Please amend paragraph [0132] of the published application as follows:

- - BIACORE~~BIAcore~~® results for certain molecules - -

Please amend paragraph [0133] of the published application as follows:

- - The numbers in Table 1D represent the IC_{50}s of the dimeric dHLX format of certain binders (molecule with antigen binding site) in the FDCP-FGFR3 proliferation assay performed with FGF9. The numbers in parentheses are the IC_{50} of the monomeric Fabs in the same assay. Table 1E presents the K_D value for certain MSPRO molecules in miniantibody form, as determined in the BIACORE~~BIAcore~~® assay. - -

Please amend paragraph [0135] of the published application as follows:

- - Certain non-limiting embodiments of molecules according to the present invention that block constitutive (ligand-independent) activation of FGFR3 are referred to herein MSPRO2, MSPRO12 and MSPRO59 comprising V_H-CDR3 and V_L-CDR3 domains having SEQ ID NO:8 and SEQ ID NO:9; SEQ ID NO:12 and SEQ ID NO:13; and SEQ ID NO:24 and SEQ ID NO:25, respectively. The preferred, but non-limiting, embodiments of molecules according to the present invention that block ligand-dependent activation of FGFR3 are referred to herein MSPRO11, MSPRO21, MSPRO24, MSPRO26, MSPRO29, and MSPRO54 comprising VH-CDR3 and VL-CDR3 domains having SEQ ID NO:10 and SEQ ID NO:11; SEQ ID NO:14 and SEQ ID NO:15; SEQ ID NO:16 and SEQ ID NO:17, SEQ ID NO:18 and SEQ ID NO:19; SEQ ID NO:21 and SEQ ID NO:22; SEQ ID NO:23 and SEQ ID NO:24, respectively. An antibody or a molecule of the present invention is said to have increased affinity for a RPTK if it binds a soluble dimeric form of said RPTK with a K_D of less than about 50 nM, preferably less than about 30 nM and more preferably less than about 10 nM, as determined by the BIACOREBIAcore® chip assay for affinity, by a FACS-Scatchard analysis or other methods known in the art. - -

Please amend paragraph [0222] of the published application as follows:

- - Both FR3exFc and FR1exFc soluble receptors were demonstrated to be expressed to a high level in transiently transfected 293T cells (T-cell antigen infected human embryonic kidney 293 cells). The observation that both soluble receptors remain bound to heparin-coated wells even following extensive washes led the laboratory of the present inventors to try to purify the proteins with the commercial HEPARIN-SEPHAROSEheparin-Sepharose® resin (Pharmacia). One hundred ml volume supernatants, harvested 48 hours post-transfection with either FR3exFc or FR1exFc coding plasmids, were incubated overnight at 4 °C. with 1 ml HEPARIN-SEPHAROSEheparin-Sepharose® resin. The resin was washed and then subjected to PBS supplemented with increasing concentration of NaCl. Aliquots of each fraction were analyzed by 7.5% SDS-PAGE stained with GELCODEGelCode® (Pierce) demonstrating a purification profile of more than 90% homogeneity and a peak elution at 400 mM NaCl for FR3exFc (FIG. 3; T=total protein, U=unbound fraction, W=wash). In contrast, FR1exFc was hardly retained on the resin. This result was confirmed by Western analysis of the same fractions with anti-

FGFR1ex antibodies demonstrating that most of FR1 exFc is in the unbound fraction (not shown). - -

Please amend paragraph [0228] of the published application as follows:

- - The screening strategies to identify Fabs from the Human Combinatorial Antibody Library (HUCAL~~HuCAL~~®, developed at MorphoSys, Munich, Germany and disclosed in WO 97/08320, U.S. Pat. No. 6,300,064, and Knappik et al., (2000), the entire contents of which are incorporated herein by reference, using soluble dimeric forms of the extracellular domain of the FGFR3 receptor are shown in Table 2. - -

Please amend paragraph [0237] of the published application as follows:

- - MAXISORP~~MaxiSorp~~® ELISA plates were coated with 100 µl anti-human Fc (10 µg/ml) in bicarbonate overnight at 4° C. Wells were washed five consecutive times with a PBS solution containing 0.1% Tween 20 (PBST). The well surface was blocked with 250 µl PBST+3% BSA (blocking solution) for 1 hour at 37° C. This was followed by capturing 1 µg of FGFR/Fc for 1 hour at room temperature. To assess the antibody binding to the captured FGFR/Fc, 1 µg each of the tested Fabs was incubated in 100 µl blocking solution per well 1 hour at room temperature. Wells were washed 5 times with PBST. Reaction was initiated with the addition of 100 µl of 0.8 µg/ml goat anti-human Fab-HRP (horseradish peroxidase) diluted in blocking solution, subsequently washed and detected with TMB substrate (Pierce). The absorbance was measured at 450 nm. A comparison of ELISA analyses done in both laboratories, Prochon and MorphoSys, is presented in **FIG. 27** and in Table 4. - -

Please amend paragraph [0240] of the published application as follows:

- - The affinity measurements were performed by BIACORE~~BIAcore~~® analysis according to the standard procedure recommended by the supplier (Pharmacia). The anti-Fc antibody was coupled via the EDC/NHS chemistry to the chip and subsequently FGFR3 was captured. The Fabs of the invention were then bound to this surface. - -

Please amend paragraph [0241] of the published application as follows:

- - Table 5 shows a comparison of affinities of Fabs candidates to FGFR3 as determined by BIACOREBIAcore® and by FACS-scatchard. - -

Please amend paragraph [0242] of the published application as follows:

- - Table 1E (in the Detailed Description, vide supra) shows the affinity as determined by BIACOREBIAcore® for the Fab candidates shown in Table 5 converted into the Fab mini-antibody format, Fab-dHLX-MH, where a dimer of the Fab monomer is produced after insertion into an expression vector as a fusion protein. - -

Please amend paragraph [0263] of the published application as follows:

- - The protein content was determined by Bradford or DC protein assay (Bio-Rad, cat# 500-0116) following manufacture instructions. Total protein aliquots, supplemented with 1/5 volume of 5Xsample buffer, were boiled for 5 minutes and stored at -20° C. until ready to load on gel. In parallel an immunoprecipitation (IP) assay was performed, 10 µl anti-FGFR3 antibodies were added to the rest of the lysates and incubated for 4 hours at 4° C. Twenty (20) ul protein A-SEPHAROSESepharose® was added and incubated for 1 hour at 4° C. with continuous shaking. Afterwards, the mixture was microcentrifuged 15 seconds, and the fluid was aspirated, carefully leaving a volume of ~30 µl above the beads. The beads were washed 3 times with 1 ml lysis buffer. At this step, the protease inhibitor mix was omitted from the buffer. - -

Please amend paragraph [0267] of the published application as follows:

- - BIACOREBIAcore® and proliferation analyses showed that among the new Fabs, MSPRO54 is highly cross reactive with FGFR1. To further test the cross reactivity of the new Fabs, RCJ cells expressing either FGFR3ach (RCJ-M14; M14 on FIG. 9A) FGFR3 wild type (W 11 on FIG. 9B), FGFR1 (R1-1 on FIG. 9C) or FGFR2 (R2-2 on FIG. 9D) were incubated with increasing amount of a control antibody LY6.3, MSPRO29, 54 and 59 for one hour. FGF9 was added for 5 minutes and cell lysates were analyzed by Western blot for ERK activation (phosphorylated ERK; pERK) (FIGS. 9A-9D). Furthermore, MSPRO13 was able to block FGFR1 activation while none of the Fabs blocked FGFR2 activation. FIGS. 9A-9D show the

results of several Fabs, at different mg concentrations, on RCJ expressing wildtype FGFR3 or the different FGFR types. MSPRO29 appeared as the best FGFR3 blocker and was also effective in blocking FGFR1 (FIG. 9c); however, MSPRO54 was the most effective Fab against FGFR1. None of the Fabs significantly inhibited FGFR2 activity. There are only a few amino acid residues within the third Ig domain that are shared by FGFR3 and FGFR1 but not by FGFR2. Making mutants at these sites should clarify their role in Fab-receptor binding. - -

Please amend paragraph [0275] of the published application as follows:

- - To determine the effect of iodination on Fab activity, 50 μg of MSPRO29 was first labeled with cold iodine using Pierce IodoGen coated tubes. The process was carried out either without iodine, with 0.04 mM NaI (low I) or with 1 mM NaI (high I). MSPRO29 was then purified through a SEPHADEX~~Sephadex~~® G-50 column. The ability of the modified Fab to bind FGFR3 was determined by ELISA. MAXISORP~~MaxiSorp~~® wells were coated with anti-human Fc. FGFR3/Fc was then anchored to the wells. In parallel, a similar set of wells was left in blocking buffer only (no FR3/Fc, hatched bars). The unmodified (no I) or the modified MSPRO29 (low or high, 2 G-50 fractions each, 1 and 2) were added at approximately 5 μg/well and binding was measured with anti-human Fab. Fresh MSPRO29 and buffer alone were included as controls (FIG. 14: FGFR3/Fc, checkered bars; no FGFR3/Fc, hatched bars). MS-PRO29 was labeled with 1 mCi ^{125}I. The specific activity of the Fab was 17 μCi/μg. - -